LETTERS TO THE EDITOR

Estimating Infection Incidence in Longitudinal Studies

To the Editor—In a longitudinal study with a maximum follow-up of more than 3 years, Vigil et al[1] found that both intermittent (IC) and persistent (PC) MRSA nares colonization increased subsequent incidence of MRSA infection and that further distinguishing between IC and PC may not improve risk prediction. The authors found increased risks of IC and PC patients in all their statistical analyses, but they also reported and compared conflicting relative frequencies of infection. The aim of this letter is to point out that the proper measure of infection incidence must lie between the numbers reported by Vigil et al., and that the statistical difficulty stems from the longitudinal design, which we believe is an asset of their study.

In their table 1, Vigil et al report so-called incidence proportions[2] (ie, the number of observed infections divided by the number of patients within colonization groups) of 11.2% (IC) and 16.3% (PC). In contrast, the proportions based on a Kaplan-Meier analysis of time-to-infection were 13% (IC) and 21% (PC).

The incidence proportions are too small. The reason is that patients were followed from study entry until infection, death, or closure of the study. Closure of the study leads to censored observations. The incidence proportions, therefore, report proportions of an observed infection. This measure does not address a patient's safety concern. For the individual patient, whether and when an infection occurs is relevant, whether this happens before administrative closure of the observational study is not. The incidence proportions are too small because the probability of the fact that an infection occurs and that it is observed is less than the probability that an infection occurs (irrespective of the observation status).

In contrast, the proportions based on the Kaplan-Meier curves are too large. The reason is that the aim of a Kaplan-Meier analysis is to approximate the incidence proportions in the absence of censoring if the incident event occurs in every patient's life, although possibly after closure of study.[3] Death is such an incident event, and a Kaplan-Meier curve is a technique from the analysis of survival data. Infections, however, may be precluded by death without prior infection, and Kaplan-Meier estimates of infection incidence overestimate the probability of infection because the method implicitly assumes that eventually all patients will be infected.[4]

The proper tool for quantifying absolute infection risks in a longitudinal study as that of Vigil et al is a generalization of the Kaplan-Meier estimator to multiple outcome types. This is the so-called Aalen-Johansen estimator, which decomposes a proper Kaplan-Meier estimator of infection-free survival into approximated proportions of infection and approximated proportions of death without prior infection.[5] Also known as cumulative incidence functions of competing risks, these curves will yield infection proportions that lie between the biased estimates reported by Vigil et al.

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Biased Low Incidence of Central Venous Catheter-Related Bloodstream Infections in Controlled Clinical Trials?

To the Editor—In the 3SITES trial,[1] the incidences of central venous catheter (CVC)-related bloodstream infections (CRBSIs) after 1:1:1 randomized catheterization of the internal

TABLE 1. Comparison of Diagnostic Criteria and Characteristics of CRBSI

Parameter	3SITES Trial (n = 2,532)	SECRECY Registry (n = 447)
Criteria for a definite CRBSI[a]		
CVC-tip colonization plus peripheral blood culture[a]	Yes	Yes
CFU cutoff for CVC colonization		
Quantitative culture[b]	1,000	No
Semiquantitative culture[b]	No	15
Differential time to positivity[a]	No	Yes
CVC catheterization, median d (range)	5 (2–9)	14 (1–60)
Definite CRBSI, no.	26	14
Definite CRBSI onset, median d	n/a	15.5
Definite CRBSI rate, %	1.0	3.1
Definite CRBSI incidence, No./1,000 CVC days	1.7	2.1

NOTE. CRBSI, central venous catheter-related bloodstream infection; CVC, central venous catheter; CFU, colony-forming units; n/a, not available.

[a]See Mermel et al[4] and Hentrich et al.[5]

[b]A CFU cutoff of 15 in semiquantitative culture is the recommended equivalent of a cutoff of 100 in quantitative culture (see Mermel et al[4] and Hentrich et al[5]).

jugular, subclavian, or femoral vein, respectively, were compared among adult intensive care unit (ICU) patients. The low total CRBSI incidence in this trial was stated to be consistent with data from other ICUs.[2] Unfortunately, however, the total CRBSI incidence was not clearly indicated in the 3SITES trial. Using the data provided,[1] we calculated a CRBSI rate of 1.0% (26 per 2,532 CVCs); for all 3 CVC insertion sites, the mean CRBSI incidence was 1.7 per 1,000 CVC days.

We believe that the reported incidence was rather low and was biased by the diagnostic criteria used.[3] For CRBSI diagnosis in the 3SITES trial, only CVC-tip colonization combined with detection of the same pathogen in peripheral blood was taken into account. Differential time to positivity of central and peripheral blood cultures was not used in the 3SITES trial.[1] However, this is a well-established parameter for CRBSI diagnosis[4] in addition to the aforementioned criterion; it is also a criterion of definite CRBSI.[3,5] Furthermore, the cutoff of colony-forming units (CFU) for CVC-tip colonization was 1,000 in quantitative culture,[1] which is higher than is usually recommended.[4,5] Instead of quantitative cultures, semiquantitative cultures with a CFU cutoff of 15 should be used for diagnosis of CVC-tip colonization.[4] However, a CFU cutoff of 15 in semiquantitative culture is the recommended equivalent of a cutoff of 100 in quantitative culture.[4,5] In addition, the median duration of CVC catheterization in the 3SITES trial was only 5 days;[1] however, CRBSIs are known to be associated with the length of CVC use in situ.[3,6]

Due to the diagnostic criteria used and the low number of CVC catheterization days, we believe the CRBSI rate and incidence, respectively, in the 3SITES trial were underestimated and do not represent a real-life setting. Therefore, we compared CRBSI data used in the 3SITE trial with CRBSI data from our SECRECY registry. SECRECY (German Clinical Trial Register No. DRKS00006551) is a real-life registry of CRBSIs in patients with hematological and oncological malignancies;[3,7] this is a high-risk population for CRBSI, comparable to the ICU patients in the 3SITES trial.

Using SECRECY data up to January 25, 2016, we report on 447 CVCs (internal jugular vein, 419 CVCs [93.7%]), which accounts for a total of 6,700 CVC days. A comparison of diagnostic criteria and characteristics of CRBSI in the 3SITES trial vs the SECRECY registry is provided in Table 1. In this real-life setting, CVCs were in situ longer and the CRBSI rate and incidence were higher than in the 3SITES trial. In the SECRECY registry, median CRBSI onset occurred on day 15.5 after CVC insertion, which is much longer than the median time the CVCs were used in situ in the 3SITES trial (ie, 5 days). Thus, the points discussed here may explain the lower CRBSI incidence in the 3SITES trial, and they should be considered when interpreting data on CRBSI in clinical trials.

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Low Incidence of Central Venous Catheter–Related Bloodstream Infections in Stem Cell Transplant Patients in Eastern India Despite High Community Burden of Multidrug-Resistant Pathogens

To the Editor—Central venous catheters (CVCs) are indispensable in hematopoietic stem cell transplant practice. With the increasing burden of multidrug-resistant bacterial organisms (MDROs) in communities worldwide, the risk of CVC colonization and subsequent life-threatening bloodstream infections (BSI) with these organisms poses a serious threat to transplant practice.[1,2] Hence, safety management of central lines presents major challenges in the setting of hematological disorders. We evaluated our experience with CVC MDRO colonization and bacteremia at the stem cell transplant (SCT) unit in the Tata Medical Center, Kolkata, India.

A retrospective cohort analysis was conducted from December 2011 to June 2015. Patients were nursed in single en-suite high-efficiency particulate air (HEPA)–filtered rooms. The air quality of each bone-marrow-transplant room was maintained using a separate air handling unit; air quality was checked using a hand-held air particle counter; air velocity was measured using an anemometer, and air pressure was monitored using a differential pressure monitor.[3] Water quality in the SCT rooms was maintained using Pall filters for shower heads and taps. These filters have a 0.2-μm pore size and provide a protective barrier against waterborne contaminants including *Legionella* spp., and *Pseudomonas* spp., and other bacteria (coliforms). The water quality of the hospital is maintained through reverse osmosis and chlorination (free chlorine, 0.2–0.5 ppm).[4]

The patient:nurse ratio in the SCT unit was 1:1.5. Nurses in the SCT unit were trained using the World Health Organization (WHO) module of hand hygiene, preparation and administration of medicines (drugs, blood products) under aseptic techniques, and CVC dressing protocol, as well as standard precautions. Housekeeping (environmental cleaning) practices included a 3-shift cleaning protocol using soap and water and sodium hypochlorite (for floors); 10% hydrogen peroxide (for all surfaces pre-admission and post discharge); and alcohol (isopropyl alcohol and ethyl alcohol for beds, steel surfaces, and biomedical equipment). Before insertion of a CVC, each patient was given a bath with 4% chlorhexidine in addition to soap and water. The CVC care bundle included sterile insertion under maximum barrier precautions, daily change of infusion sets, gauze or transparent dressing, flushing and locking, as well as the use of an ELD96 filter (Pall) for total parenteral nutrition and a Lipipor filter (Pall) for parenteral lipids. We also used a leucodepletion filter for packed cells and platelets. A dose of antibiotic (co-amoxiclav) was given pre-operatively within 60 minutes of CVC insertion. CVCs were inserted a few days prior to transplant, and where feasible, most CVCs were removed within 90 days of insertion. Skin preparation before insertion was done using 2.5% chlorhexidine with isopropyl alcohol 70% (or 10% povidone iodine). Patients and family members were educated to take care of the central line at home and to report to the outpatient department for heparinized flushing, blood sampling, and dressing weekly. Before accessing the line, meticulous hub scrubbing was done for 20–30 seconds with 2.5% chlorhexidine and 70% isopropyl alcohol. The line sites were evaluated on every shift for signs of inflammation and infection of the exit site. Bed linens for each the patient were sterilized by autoclaving and changed daily. Patients were provided with a "neutropenic diet" (pressure cooked food and water). Stem cells were collected, stored, and infused under aseptic techniques. All cases of clinical sepsis and positive blood cultures were proactively treated using a protocol of empirical therapy (piperacillin-tazobactam + amikacin > meropenem + teicoplanin > meropenem + colistin), and positive blood culture directed early therapy based on Gram-stain findings and preliminary sensitivity.[5]

During the study period, a total of 170 CVCs were placed in 163 patients to support 172 transplants, including 112 allogeneic procedures. Nearly one-third of allogeneic transplants (36 of 112) were high risk, including HLA haplotype–matched procedures (28 of 112) and matched–unrelated donor procedures (8 of 112). The median age of patients was 32 years (range, 2–66 years), 123 (75%) were male. The majority of CVCs were tunneled devices (Hickman catheters; 113 of 170); the rest were peripherally inserted central lines (PICCs; 10 of 170) and non-tunneled central lines (47 of 170) inserted into jugular or subclavian veins. Pre-transplant surveillance cultures of stool and throat swabs identified MDROs in 145 (87%) and 42 (26%) patients, respectively.[6] Stool surveillance showed ESBL in 87 patients (60%), carbapenemase producers in 43 patients (30%), AmpC producers in 26 patients (18%), and VRE in 4 patients (2.7%). Throat surveillance showed carbapenemase producers in 23 patients tested (55%), ESBL in 17 patients (40%), AmpC producers in 4 patients (9.5%), and VRE in 1 patient (2.3%) (Table 1).

The median duration of neutropenia ($\leq 500/mm^3$) was 11 days (3–36 days). A cumulative 11,410 CVC days were recorded, with a median 58 days per patient (range, 8–418 days, interquartile range, 18–89 days). A total of 36 BSIs were observed, including 9 isolates identified in pre-transplant

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